DRAFT

July 05, 2002

STANDARD OPERATING PROCEDURE FOR METABOLISM ASSESSMENT REVIEW COMMITTEE

I. Purpose of Metabolism Assessment Review Committee (MARC)

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A. Mission

The mission of the Metabolism Assessment Review Committee (MARC) is to:

1. Determine the metabolites and/or breakdown products which should be included in the dietary exposure/risk assessment and/or tolerance expression for foods and livestock feeds.
2. Determine the degradates which should be included in the risk assessment for ingestion of ground and surface water.
3. Provide a recommendation on the hazard of degradates and/or metabolites relative to the parent (i.e., toxicity is equal, less than, or greater than the parent).
4. Provide advice on whether additional metabolism data should be submitted or whether toxicology data should be submitted on metabolites, breakdown products, or degradates.

B. Criteria for Convening MARC Meetings

All new active ingredients should be considered for presentation to the MARC upon review of their first food use. In the case of pesticides undergoing reregistration or tolerance reassessment, the risk assessment team members should use their judgment and decide on a case-by-case basis whether significant changes have occurred in residues (levels, identities) or the toxicological endpoints which would merit a new examination by the Committee. If the plant and livestock metabolism has been elucidated, a MARC meeting may be needed to provide guidance to the Environmental Fate and Effects Division (EFED) on the degradates to be included in a drinking water assessment.

Upon determining that the radiolabeled plant, livestock, and/or rotational crop studies, as applicable, adequately describe the metabolism of the pesticide, the residue chemist should confer with the toxicologist reviewing the chemical to determine if review by the Committee is needed. Ideally, the toxicological data base should be complete and the Hazard Identification Committee (HIARC) has determined the endpoints of concern. However, if the acceptability of residue chemistry studies is hinging on a decision for the residue of concern or a registrant holding samples for analysis needs a preliminary decision, the chemist and toxicologist may need to proceed regardless of the status of the toxicological review.

Most new food use pesticides (or reregistration/reassessment chemicals with significant changes in residue identities or toxicological endpoints) will require a meeting of the full Committee. However, for a limited number of situations, two alternatives to a full committee meeting are available: 1) electronic review by the entire MARC; or 2) a risk assessment team meeting with the MARC chair and his/her designees. Good examples of this scenario would be a pesticide

where the parent compound comprises virtually all the radioactive residue and cases where the only identified metabolites represent reincorporation into natural products. If the team concludes that a meeting with the entire Committee is necessary, they should proceed as described in Section II with scheduling and preparation of the briefing documents. If they believe the alternative, shortened procedures are appropriate, a member of the RAT should confer with the MARC Chair to determine which course of action is appropriate. **WHEN DO YOU CHOOSE AN ELECTRONIC MEETING AND WHEN IS A RAT MEETING APPROPRIATE. NOTE THAN E MARC MEETING IS NOT APPROPRIATE FOR SHORTENING THE PROCESS, AND MAY IN FACT LENGTHEN THE PROCESS FOR DIFFICULT CHEMICALS**

The risk assessment team meeting should include the Chair of the Committee, other MARC members designated by the Chair, and a representative from EFED should also attend to explain which residues are likely to be found in ground and surface water. The metabolic pathways in plants and the rat as well as, if applicable, livestock and rotational crops should be examined in the risk assessment team meeting along with known toxicological properties of the pesticide. Formal briefing memos do not need to be prepared for these meetings. For example, handwritten summaries of metabolism studies and likely toxicological endpoints in addition to copies of key chemical structures may be sufficient. A decision to have a meeting of the full Committee will result if any of the following are observed:

1. The presence of a metabolite/degradate at significant levels in food/feed that is not included in the proposed tolerance expression or petitioner's risk assessment.
2. The presence of a residue at significant levels in food/feed that is not found in the rat metabolism study.
3. A metabolite/degradate is suspected to be significantly more toxic than the parent pesticide.
4. The proposed tolerance expression differs from that used by Codex, Canada, or Mexico.
5. The presence of a metabolite/degradate in water that is not included in the proposed tolerance expression or petitioner's risk assessment.

If one or more of the above conditions are met, the risk assessment team should notify the Executive Secretary of the need for a meeting of the full Committee along with a time frame by which the briefing document can be prepared.

If the attendees at the risk assessment team meeting agree that the petitioner's proposed residue of concern is reasonable, a decision memorandum should be prepared by the risk assessment team for concurrence by the Chair and all Committee members in attendance. While this document need not be as detailed as the briefing memo for a full Committee meeting, sufficient information must be included to document the decision. At a minimum items *b* and *g* from the

residue chemistry section of a briefing memo (i.e., summary of the metabolic pathways and Codex considerations) and the major toxicological endpoints need to be addressed. These are detailed later in this SOP in section II.B. on the format of briefing documents. The MARC Chair will sign the document prepared after the team meeting once all attendees and the branch senior scientist agree on its content. See section IV.4. for the "From/Thru/To" format of this memorandum.

C. Composition of MARC

The MARC shall be composed of a Chairperson, an Executive Secretary, HED toxicologists, HED chemists all designated by HED management; and an EFED representative designated by EFED management.

1. Responsibilities of Chairperson

The Chairperson will be designated by HED management. The Chair will be responsible for conducting the meeting and ensuring that a consensus has been reached. If the Chair is unable to attend a meeting, he/she shall designate an alternate to act on his/her behalf. The Chair will also sign all memoranda documenting Committee decisions.

2. Responsibilities of Executive Secretary

The Executive Secretary will be responsible for scheduling all meetings of the MARC, securing meeting rooms, informing members of meetings, distributing copies of the briefing memorandum, taking meeting minutes and attendance, and reporting MARC activities to the HED weekly report. The Secretary is also responsible for maintaining a paper file of briefing and decision documents and for placing electronic files of the same in the Committee's directory on the LAN. If the Executive Secretary is unable to temporarily fulfill his/her duties, the Chair will consult with HED management as appropriate to select an alternate.

II. Preparation for Meeting

A. Scheduling the Meeting

When the toxicology and chemistry reviewers determine that the MARC should be convened, one of the reviewers or the Branch Senior Scientist shall contact the Executive Secretary of the MARC and inform the Executive Secretary of the need for a meeting, the desired meeting date, and the Division due date for the chemical (if one has been established).

B. Briefing Memorandum

A briefing memorandum shall be submitted by the requesting branch to the Executive Secretary no later than seven business days before the scheduled meeting. The briefing memorandum shall consist of an introduction, residue chemistry section, a toxicology section, and water chemistry section as described below. This memorandum should be "From" the lead chemist and lead toxicologist, "Through" their branch senior scientist(s), and "To" the Executive Secretary of the MARC. The title should include the words "Briefing Memorandum" to facilitate electronic searching of the document. In addition to the original paper version, the Executive Secretary should receive a disk with the briefing memorandum file named in the following format:

D123456.MEM.WPD

The Executive secretary will forward the file to the IMCSB storage gate-keeper for placement in the chemical's subdirectory. The Executive Secretary will circulate an electronic copy of the briefing memorandum to all committee members to accommodate those on flexiplace.

Note that highly detailed descriptions are not needed in the briefing memorandum except as noted below. The MARC is relying upon the members of the risk assessment team to summarize the critical points in support of the proposal and questions to the committee. Detailed supporting memoranda, such as residue chemistry chapters/DERS, should be brought to the meeting if there are any specific questions. Lengthy briefing memoranda will be returned to the risk assessment team and the meeting will be delayed until an appropriate document is submitted to the MARC.

1. Introduction

The introductory section of the memorandum should include the following information. A generic example is included in Attachment 1 to this SOP.

a. Identification of chemical

The memorandum should begin with a description of the chemical, commodities of interest, and the tolerance levels proposed by the petitioner. If the pesticide is a reregistration chemical, or has previously established tolerances, then a listing of all existing and proposed tolerances should be included. However, if the pesticide is used on numerous crops, a listing of representative crops and/or crop groups is sufficient.

b. Issues for the Committee

The briefing memorandum should include specific questions the review team is asking the MARC to consider. This is particularly important when a chemical is being considered multiple times so the MARC can focus on specific issues.

c. Chemical Team Proposal

The chemical team should provide a proposal of the metabolites and degradates that should be included in the tolerance expression and risk assessment in a tabular format. Brief notes on the proposal should follow the table.

2. Residue Chemistry Section

The residue chemistry portion of the briefing document for the Committee should include the following information.

a. Use Information

Use of the pesticide should be described, including: type of pesticide (e.g., herbicide, insecticide), the basic use pattern (foliar or soil application; range of application rates and pre-harvest intervals), pests controlled, and the crops to be treated.

b. Physical/Chemical Properties

A brief discussion of the physical/chemical properties of the parent compound (and metabolites or degradates, if known) including physical state, solubility, and octanol/water partition coefficient (K_{ow}).

c. Summary of Plant and Livestock Metabolism Studies

The mode, rate and number of applications should be listed along with the pre-harvest or pre-slaughter interval. Significant differences between these parameters and the proposed usage of the pesticide should be highlighted. A tabular summary should be presented for each study (or group of studies if limited number of matrices examined) showing the ppm and % of the total radioactive residue (TRR) for each identified and characterized residue. Chemical structures must be presented for each identified component, preferably as part of a flowchart outlining the metabolic pathways. A detailed description of the identification procedures should not be included in the summary, unless in the reviewer's opinion it will be needed by the MARC to make a decision on the adequacy of the database. Extraction procedures need only be described very briefly with emphasis on techniques tried to release bound residues and to characterize unidentified residues by their solubility or partitioning characteristics.

d. Rotational Crop Studies

If the confined rotational crop studies show identifiable residues above the level of 0.01 ppm at any plantback interval, tabular summaries and chemical structures should be presented as described in item *c*.

e. Residue Analytical Methods

Brief descriptions of analytical methods (e.g., GC/MS, HPLC/UV) along with the residues which are measured should be provided. It should be indicated whether the analytes are measured individually or converted to a common moiety, and whether conjugates could be analyzed. Results of radiovalidations should also be briefly described. A detailed summary of forition recovery data should not be included in the summary.

f. Multiresidue Methods

Available data on the ability or inability of FDA's multiresidue methods to detect and recover the

parent pesticide and metabolites should be summarized.

g. Crop Field Trials and Livestock Feeding Studies

Such studies should be summarized, preferably in tabular form, if they contain data on relative levels of parent pesticide and metabolites in plants and livestock commodities, respectively.

h. International Considerations

The document should state whether any Codex, Canadian, or Mexican MRL's or tolerances are established or proposed and the specific residue(s) covered by such regulations. If it is likely that the residue to be regulated or included in the risk assessment will be different from that which is regulated by Codex, then the document should state whether Codex includes information on such residues in their monographs.

4. Toxicology Section

a. Toxicological Endpoints

The briefing document should include a summary of the toxicology endpoints (acute, chronic and cancer) for dietary risk assessment. This section should also state any concerns about mutagenicity, neurotoxicity, or developmental toxicity produced by the pesticide. If the Hazard ID report has been finalized, the table summarizing all endpoints would be appropriate for inclusion. If the HIARC has not met, the toxicologist should estimate endpoints based on his/her knowledge of this chemical and other similar chemicals.

b. Rat Metabolism

A summary of all rat metabolism studies should be included in the briefing memorandum, and should specifically highlight the significant metabolites identified in rat excreta and tissues (if available). The relative amount of each metabolite found should be summarized in a table. Metabolites that are found in plants, water, and/or livestock that are not found in the rat should be highlighted. A copy of the metabolic pathway should be included in the memorandum as well.

5. Residues in Water Section

If the MARC is being asked to consider the degradates of concern in drinking water, then the briefing memorandum must include a section on the environmental fate of the parent pesticide. Listed below are a series of questions that should be answered in the water section of the memorandum.

1.) Briefly describe the environmental persistence of the pesticide. What are expected to be the major routes of degradation in the environment (e.g. aerobic soil metabolism, soil photolysis, etc)? What is the expected persistence in soil and water (provide available half lives)?

2.) Briefly describe the expected mobility of the pesticide. Is the pesticide volatile? Does the pesticide bind soil or sediment strongly (please provide Kd or Koc)?

3.) Briefly describe the degradates of the pesticide. Identify major and minor degradates. Provide available information degradate stability and mobility.

4.) In your opinion, what degradates will most likely be found in drinking water? Please consider the crops that are currently registered, as well as those proposed for registration. Please exercise your best judgement as to what would most likely be present, not necessarily listing all those that could theoretically be present. Has any specific environmental fate data been submitted for these degradates?

5.) Provide any other pertinent information (e.g. monitoring data).

6.) If possible, describe the effects of water treatment on the pesticide and degradates that may reach drinking water sources.

7.) Has the Office of Water or any other regulatory body set an action level on the parent or degradates?

8.) Complete the following table. For each study type, include the percent of applied dose. **(NOTE TO MARC MEMBERS: SHOULD WE GO AHEAD AND LIST THE STUDIES FOR THEM. I.E. AEROBIC SOIL METABOLISM, PHOTOLYSIS, ETC. SEE DEGRADATE 2 AS AN EXAMPLE.)**

Degradate Name and Structure	Percent of Applied Dose	Study	Comments
Parent			e.g. Half Life
Degradate 1			e.g. Half Life
Degradate 2		Aerobic Soil Metabolism (GLN No.)	
		Field Dissipation	

Degradate Name and Structure	Percent of Applied Dose	Study	Comments
		Photolysis	
		Anaerobic Aquatic Metabolism	
Degradate 3			

C. Toxicology Briefing Materials

To assist the Committee in its deliberations, the lead toxicologist for the chemical should bring copies of the following documents to the MARC meeting (when available):

1. HIARC Committee Report or 1-liners and/or revised Executive Summaries for old chemicals.
2. Cancer SARC Report.
3. Data on the toxicity of metabolites (For example in 1-liners and/or computerized data bases).
4. For older chemicals include the RfD and TES Report (if the HIARC Committee report is not available).
5. A copy of the DER for the rat metabolism study (in particular information on metabolic pathways and metabolite abundances).
6. Any pertinent rebuttals or position papers submitted by the registrant concerning the toxicity of the parent or its metabolites.
7. If new toxicology studies have been submitted by the registrant as a result of a previous MARC decision, the lead toxicologist should bring the respective DERs.

III. MARC Meeting

A. Responsibilities of Lead Chemist

The lead chemist should attend the MARC meeting; if unable to attend he/she should designate a person familiar with the chemical to brief the MARC on his/her behalf. The chemist should be able to provide any additional details of the residue chemistry studies not included in the briefing memorandum. If a preliminary dietary risk assessment has been completed, the lead chemist or

lead toxicologist should be familiar with the results or request that the risk assessor for the pesticide also attend the MARC meeting.

B. Responsibilities of Lead Toxicologist

The lead toxicologist should attend the MARC meeting; if unable to attend he/she should designate a person familiar with the chemical to brief the MARC on his/her behalf. Participation of the lead toxicologist in the meeting deliberations might include commenting on any of the following topics:

1. Identification of endpoints driving the risk assessment of the parent chemical and/or its metabolites.
2. Carcinogenicity, mutagenicity, neurotoxicity, or developmental toxicity concerns, if any.
3. Status of the toxicity database on the chemical.
4. Are any of the plant or livestock metabolites or water degradates listed in the briefing memo absent in the rat metabolism study?
5. Are there any data available on the mode of toxic action of the chemical?
6. Are there any toxicological data available on the metabolites?

C. Responsibilities of EFED Representative

A representative from EFED shall be prepared to provide any additional information on the degradates of the subject pesticide in water if the review team is asking the MARC to consider which degradates should be included in the human dietary risk assessment.

D. Responsibilities of MARC Executive Secretary

The MARC Executive Secretary will take minutes of the meeting using a flipchart or other means. A copy of the meeting minutes will be provided within two business days to the chemical team. The Executive Secretary will also provide the chemical team a TXR number to be put on the cover page of the decision memorandum.

IV. Decision Memorandum

The review team shall prepare a memorandum summarizing the deliberations of the Committee and the final decision. The team shall decide amongst themselves which member has the final responsibility for preparing the memorandum.

A. Format of Memorandum

The decision memorandum shall have the following sections:

1. Attendance

A listing of members and responsible scientists present at the meeting. For electronic MARC meetings the attendance section will include a list of MARC members who provided comments on the team proposal.

2. Signature Authority

The document should be "From" the lead toxicologist and lead chemist; addressed "To" the Executive Secretary of the MARC; and be "Thru" the Branch Senior Scientist of the lead author of the memorandum and the Chair of the MARC.

3. TXR Number on Cover Page

SIMB will add a TXR number during the finalization process

4. Introduction

A summary of the issues considered by the MARC. The summary will also include the date of the meeting or the date the electronic meeting was initiated.

5. Material Reviewed

A brief description of the documents reviewed by the MARC during the decision-making process. This would include any e-mails and information presented during the meeting.

6. MARC Decision Table

The document should include a table summarizing the MARC decision. The format is shown below.

Table 1. Summary of MARC Desision for [*Chemical Name*] from Meeting on [*Date*]

Matrix	Residues included in Tolerance Expression	Residues included in Risk Assessment
Plants	Parent, M1	Parent, M1
Livestock	Parent, M1	Parent, M1, M2
Rotational Crops	Not applicable	Parent, M1
Water	Not Applicable	Parent, M1, D4

7. MARC Decision Rationale

The document should include a section with the decisions made in response to the Questions to the Committee and the rationale for these conclusions. This section should have sub-categories for each matrix and should describe the considerations that the MARC employed when making their decision. Detailed information from the briefing memorandum should NOT be included.

B. Secondary Review of Decision Memorandum

The decision memorandum shall be reviewed by the Branch Senior Scientist (BSS) of the principal author of the decision memorandum. Once the lead author has modified the memorandum according to the instructions of the BSS, the author shall distribute a draft to the MARC members via electronic mail. Unless there are time constraints noted in the cover memorandum, the MARC members shall have three business days to comment on the draft. If no comments are received the author shall notify the Chair that no comments were made and they shall make a decision whether the memorandum should be finalized. If the author disagrees with any comments received, he/she shall notify the Chair of the MARC and the BSS of his/her concerns and they shall make a decision on how the comments should be incorporated into the final memorandum.

C. Finalizing the Decision Memorandum

Once the decision memorandum has been edited, the lead author will give an electronic copy of the memorandum to the IMCSB SARC gatekeeper, Josephine Brooks. She will add a TXR number and obtain signatures on the final document. IMCSB is also responsible for copying the final document and distributing each copy, and filing the final document electronically. The Executive Secretary shall maintain a file with the originals of all briefing and decision memoranda. Each original decision memo should have the corresponding briefing memorandum attached in the MARC file.

ATTACHMENT 1. Example Introduction

[*Common name of chemical] [optional: chemical name]* is a new herbicide with pending uses on peanuts, apples, and corn. The registrant has proposed the following tolerances for the combined residues of the parent compound and the metabolite M1:

Peanuts	0.1 ppm
Apples	0.01 ppm
Corn	0.05 ppm
Meat (cattle, etc)	0.05 ppm
Meat by-products	0.1 ppm

Issues to be Considered:

- Residues to be included in risk assessment and tolerance expression for plants.
- Residues to be included in risk assessment and tolerance expression for livestock
- Residues of concern in rotational crops.
- Degradates of concern in water.

Proposal

[*Branch*] proposes the following:

Table 1. Residues of Concern for [*New Chemical*]

Matrix	Residues included in Tolerance Expression	Residues included in Risk Assessment
Plants	Parent, M1	Parent, M1
Livestock	Parent, M1	Parent, M1, M2
Rotational Crops	Not applicable	Parent, M1
Water	Not Applicable	Parent, M1, D4

Notes on Proposal:

- M1 is the major metabolite found in corn stover, corn grain, apples, and peanut nutmeats (refer to tables x, y, and z).
- M2 is found in milk, liver, and kidney at levels exceeding 10% of the TRR. However the registrant has not been able to develop an adequate enforcement method, so should not be

included in the tolerance expression (refer to table zz).

- M1 are the major metabolites found in rotational crops. Rotational crop tolerances are not needed at this time based on the proposed plant-back interval of 30 days.
- M3 is a major metabolite in peanut nutmeat. We have not recommended for inclusion in the risk assessment because it is not likely to contribute to the toxic effects of concern.
- D4 is not a rat metabolite, was found at levels <2% of the TRR in plants, and was found in the aerobic soil metabolism studies at levels 20-60% of the total residue (refer to table 7, p. xx).

Matrix	Major Metabolites/Degradates Found [1]	Minor Metabolites/Degradates [2]
Crop 1		
Crop 2		
Crop 3		
Ruminants		
Milk		
Poultry		
Eggs		
Rats		
Rotational Crops		
Water		

[1] Major is defined as comprising >10% of the total radioactive residues in a plant or livestock metabolism study, or as >10% of the applied dose in an environmental fate study.

[2] Minor is defined as comprising <10% of the total radioactive residues in a plant or livestock metabolism study, or as <10% of the applied dose in an environmental fate study.

6/23/98

STANDARD OPERATING PROCEDURE FOR METABOLISM ASSESSMENT REVIEW COMMITTEE

I. Purpose of Metabolism Assessment Review Committee (MARC)

A. Mission

The mission of the Metabolism Assessment Review Committee (MARC) is to:

1. Determine the metabolites and/or breakdown products which should be included in the risk assessment and/or tolerance expression for foods and animals feeds.
2. Determine the degradates which should be included in the risk assessment for ingestion of ground and surface water.
3. Provide a recommendation on the hazard of the degradate relative to the parent (i.e., equally, less than, or greater than the parent).
4. Provide advice on whether additional metabolism data should be submitted or whether toxicology data should be submitted on metabolites, breakdown products, or degradates.

B. Criteria for Convening MARC Meetings

All new active ingredients should be considered for presentation to the MARC upon review of their first food use. In the case of pesticides undergoing reregistration or tolerance reassessment, reviewers should use their judgment and decide on a case-by-case basis whether significant changes have occurred in residues (levels, identities) or the toxicological endpoints which would merit a new examination by the Committee.

Upon determining that the radiolabeled plant, livestock, and/or rotational crop studies, as applicable, adequately describe the metabolism of the pesticide, the residue chemist should confer with the toxicologist reviewing the chemical to determine if review by the Committee is needed. Ideally, the toxicological data base should be complete and the Hazard ID Committee previously determined the endpoints of concern. However, if the acceptability of residue chemistry studies is hinging on a decision for the residue of concern or a registrant holding samples for analysis needs a preliminary decision, the chemist and toxicologist may need to proceed regardless of the status of the toxicological review.

Most new food use pesticides (or reregistration/reassessment chemicals with significant changes in residue identities or toxicological endpoints) will require a meeting of the full Committee. However, in some instances an ad hoc meeting with a portion of the MARC may be sufficient. Good examples of this scenario would be a pesticide where the parent compound comprises virtually all the radioactive residue and cases where the only identified metabolites represent reincorporation into natural products. If the reviewers conclude that a meeting with the entire Committee is necessary, they should proceed as described in Section II with scheduling and preparation of the briefing documents. If they believe there is a reasonable chance the full Committee does not need to be involved, an ad hoc meeting with a portion of the Committee

may be arranged. If the reviewers have questions on how to proceed, they should confer with the MARC Chair.

The attendees at an ad hoc meeting should include the Chair of the Committee and a representative from EFED should also attend to explain which residues are likely to be found in ground and surface water. Other staff such as the reviewers' branch senior scientist(s) and/or one or two MARC members in addition to the Chair may also be included in this preliminary meeting. The metabolic pathways in plants and the rat as well as, if applicable, livestock and rotational crops should be examined in the ad hoc meeting along with known toxicological properties of the pesticide. Formal briefing memos do not need to be prepared for these ad hoc meetings. For example, handwritten summaries of metabolism studies and likely toxicological endpoints in addition to copies of key chemical structures may be sufficient. A decision to have a meeting of the full Committee will result if any of the following are observed:

1. The presence of a metabolite/degradate at significant levels in food/feed that is not included in the proposed tolerance expression or petitioner's risk assessment.
2. The presence of a residue at significant levels in food/feed that is not found in the rat metabolism study.
3. A metabolite/degradate is suspected to be significantly more toxic than the parent pesticide.
4. The proposed tolerance expression differs from that used by Codex, Canada, or Mexico.
5. The presence of a metabolite/degradate in water that is not included in the proposed tolerance expression or petitioner's risk assessment.

If one or more of the above conditions are met, the reviewers should notify the Executive Secretary of the need for a meeting of the full Committee along with a time frame by which the briefing document can be prepared. In the case of item 3, the scientists may wish to consult with toxicologists on the Committee to see if the issue can be resolved without a formal meeting of the full Committee.

If the attendees at the ad hoc meeting agree that the petitioner's proposed residue of concern is reasonable, a rationale for not needing a Committee meeting should be prepared by the reviewers for concurrence by the Chair and all Committee members in attendance. While this document need not be as detailed as the briefing memo for a full Committee meeting, sufficient information must be included to document the decision. At a minimum items *b* and *g* from the residue chemistry section of a briefing memo (i.e., summary of the metabolic pathways and Codex considerations) and the major toxicological endpoints need to be addressed. These are detailed later in this SOP in section II.B. on the format of briefing documents. The MARC Chair will sign the document prepared after the ad hoc meeting once all attendees agree on its content. See section IV.4. for the "From/Thru/To" format of this memorandum.

C. Composition of MARC

The MARC shall be composed of a Chairperson, an Executive Secretary, HED toxicologists designated by HED management, HED chemists designated by HED management, and an EFED representative designated by EFED management.

1. Responsibilities of Chairperson

The Chairperson will be selected by consensus by the MARC. The Chair will be responsible for conducting the meeting and ensuring that a consensus has been reached. If the Chair is unable to attend a meeting, he/she shall designate an alternate to act on his/her behalf. The Chair will also sign all memoranda documenting Committee decisions.

2. Responsibilities of Executive Secretary

The Executive Secretary will be responsible for scheduling all meetings of the MARC, securing meeting rooms, informing members of meetings, distributing copies of the briefing memorandum, and taking attendance at the meeting. The Secretary is also responsible for maintaining a paper file of briefing and decision documents and for placing electronic files of the same in the Committee's directory on the LAN. If the Executive Secretary is unable to temporarily fulfill his/her duties, the Chair will consult with HED management as appropriate to select an alternate.

II. Preparation for Meeting

A. Scheduling the Meeting

When the toxicology and chemistry reviewers determine that the MARC should be convened, one of the reviewers or the Branch Senior Scientist shall contact the Executive Secretary of the MARC and inform the Executive Secretary of the need for a meeting, the desired meeting date, and the Division due date for the chemical (if one has been established).

B. Briefing Memorandum

A briefing memorandum shall be submitted by the requesting branch to the Executive Secretary no later than five business days before the scheduled meeting. The briefing memorandum shall consist of a residue chemistry section, a toxicology section, and water chemistry section as described below. This memorandum should be "From" the lead chemist and lead toxicologist, "Thru" their branch senior scientist(s), and "To" the Executive Secretary of the MARC. In addition to the original paper version, the Executive Secretary should receive a disk with the briefing memorandum file named in the following format:

T:\HED\REVIEWS*pccode*\CHEM\D123456.MEM

The Executive secretary will forward the file to the IMCSB storage gate-keeper for placement in the chemical's subdirectory.

1. Residue Chemistry Section

The residue chemistry portion of the briefing document for the Committee should include the following information.

a. Use Information/Identification of Chemical

The type of pesticide (e.g., herbicide, insecticide), the basic use pattern (foliar or soil application; range of application rates and pre-harvest intervals), crops to be treated, and the range of proposed tolerance levels including any for livestock commodities (especially milk). If the pesticide is a reregistration chemical, then a listing of all existing and proposed tolerances should be included. However, if the pesticide is used on numerous crops, a listing of representative crops and/or crop groups is sufficient.

b. Summary of Plant and Livestock Metabolism Studies

The mode, rate and number of applications should be listed along with the pre-harvest or pre-slaughter interval. Significant differences between these parameters and the proposed usage of the pesticide should be pointed out. A tabular summary should be presented for each study (or group of studies if limited number of matrices examined) showing the ppm and % of the total radioactive residue (TRR) for each identified and characterized residue. Chemical structures must be presented for each identified component, preferably as part of a flowchart outlining the metabolic pathways. A detailed description of the identification procedures should not be included in the summary, unless in the reviewer's opinion it will be needed by the MARC to make a decision. Extraction procedures need only be described briefly with emphasis on techniques tried to release bound residues and to characterize unidentified residues by their solubility or partitioning characteristics.

c. Rotational Crop Studies

If the confined rotational crop studies show identifiable residues above the level of 0.01 ppm at the plantback intervals desired by the registrant, tabular summaries and chemical structures should be presented as described in item *b*.

d. Residue Analytical Methods

Brief descriptions of analytical methods (e.g., GC/MS, HPLC/UV) along with the residues which are measured should be provided. It should be indicated whether the analytes are measured individually or converted to a common moiety, and whether conjugates could be analyzed. Results of radiovalidations should also be briefly described.

e. Multiresidue Methods

Available data on the ability or inability of FDA's multiresidue methods to detect parent pesticide and metabolites should be summarized.

f. Crop Field Trials and Livestock Feeding Studies

Such studies should be summarized, preferably in tabular form, if they contain data on relative levels of parent pesticide and metabolites in plants and animals, respectively.

g. International Considerations

The document should state whether any Codex, Canadian, or Mexican MRL's or tolerances are established or proposed and the specific residue(s) covered by such regulations. If it is likely that the residue to be regulated or included in the risk assessment will be different from that which is included in Codex, then the document should state whether Codex includes information on such residues in their monographs.

2. Toxicology Section

The briefing document should include a summary of the toxicology endpoints (acute, chronic and cancer) for dietary risk assessment. This section should also state any concerns about mutagenicity, neurotoxicity, or developmental toxicity produced by the pesticide. If the Hazard ID report has been finalized, the table summarizing all endpoints would be appropriate for inclusion. If the Hazard ID has not met, the toxicologist should estimate endpoints based on his/her knowledge of this chemical and other similar chemicals. The significant metabolites in rat excreta and tissues (if available) should be indicated. Any metabolites or degradates found in plants, livestock or water, but not in the rat, should be pointed out.

3. Residues in Water Section

The briefing document should include a brief description of the degradates found in ground and surface water and the relative proportion of each unless the Committee has addressed water degradates previously. If the Office of Water or any other regulatory body has set an action level, maximum residue limit, or other regulatory level on the parent or degradate, such information should be included as well. The lead toxicologist or lead chemist shall be responsible for obtaining this information from EFED.

4. Questions to the Committee

The briefing memorandum should include questions the review team is asking the MARC to consider.

C. Toxicology Briefing Materials

To assist the Committee in its deliberations, the lead toxicologist for the chemical should make available to the Committee's Executive Secretary, for consideration during the meeting, copies of the following documents (when available):

1. Hazard ID Committee Report or 1-liners and/or revised Executive Summaries for old chemicals.
2. Cancer SARC Report (Don't include the whole report, just the carcinogenicity classification and its rationale and any mechanistic and SAR information).
3. Data on the toxicity of metabolites (For example in 1-liners and/or computerized data bases).
4. For older chemicals include the RfD and TES Report (if the Hazard ID Committee report is not available).
5. A copy of the DER for the rat metabolism study (in particular information on metabolic pathways and metabolite abundances).
6. Any pertinent rebuttals or position papers submitted by the registrant concerning the toxicity of the parent or its metabolites.
7. If new toxicology studies have been submitted by the registrant as a result of a previous MARC decision, the lead toxicologist should make available the respective DERs or a brief summary of the data to the Executive Secretary.

III. MARC Meeting

A. Responsibilities of Lead Chemist

The lead chemist should attend the MARC meeting; if unable to attend he/she should designate a person familiar with the chemical to brief the MARC on his/her behalf. The chemist should be able to provide any additional details of the residue chemistry studies not included in the briefing memorandum. If a preliminary dietary risk assessment has been completed, the lead chemist or lead toxicologist should be familiar with the results or request that the risk assessor for the pesticide also attend the MARC meeting.

B. Responsibilities of Lead Toxicologist

The lead toxicologist should attend the MARC meeting; if unable to attend he/she should designate a person familiar with the chemical to brief the MARC on his/her behalf. Participation of the lead toxicologist in the meeting deliberations might include commenting on any of the following topics:

1. Identification of endpoints driving the risk-assessment of the parent chemical and/or its metabolites.

2. Carcinogenicity, mutagenicity, neurotoxicity or developmental toxicity concerns, if any.
3. Status of the database on the chemical. Any new testing?
4. Are any of the plant or animal metabolites or water degradates listed in the briefing memo absent in the rat metabolism study?
5. Are there any data available on the mode of toxic action of the chemical?
6. Are there any toxicological data available on the metabolites?

C. Responsibilities of EFED Representative

A representative from EFED shall be prepared to provide any additional information on the degradates of the subject pesticide in water if the review team is asking the MARC to consider which degradates should be included in the human dietary risk assessment.

IV. Decision Memorandum

The review team shall prepare a memorandum summarizing the deliberations of the Committee and the final decision. The team shall decide amongst themselves which member has the final responsibility for preparing the memorandum.

A. Format of Memorandum

The decision memorandum shall have the following sections:

1. Attendance

A listing of members and responsible scientists present at the meeting.

2. Summary of Deliberations

A summary of the issues considered by the MARC.

3. MARC Decision

The document should include a section with the decisions made in response to the Questions to the Committee and the rationale for these conclusions.

4. Signature Authority

The document should be "From" the lead toxicologist and lead chemist; addressed "To" the Executive Secretary of the MARC; and be "Thru" the Branch Senior Scientist of the lead author of the memorandum and the Chair of the MARC.

B. Secondary Review of Decision Memorandum

The decision memorandum shall be reviewed by the Branch Senior Scientist (BSS) of the principal author of the decision memorandum. Once the lead author has modified the memorandum according to the instructions of the BSS, the author shall distribute a draft to the MARC members via electronic mail. Unless there are time constraints noted in the cover

memorandum, the MARC members shall have three business days to comment on the draft. If no comments are received the author shall notify the Chair that no comments were made and they shall make a decision whether the memorandum should be finalized. If the author disagrees with any comments received, he/she shall notify the Chair of the MARC and the BSS of his/her concerns and they shall make a decision on how the comments should be incorporated into the final memorandum.

C. Finalizing the Decision Memorandum

1. Paper Copies

The lead author should ensure that the lead toxicologist, the lead chemist, and the lead from the risk management division responsible for initiating the action are all listed to receive copies of the decision memorandum. Committee members do not need to receive copies. It is also not necessary to attach a copy of the briefing memorandum to the copies of the decision memorandum. Once all signatures have been obtained on the decision memo, the lead author's branch is responsible for preparing and distributing the necessary number of copies. The original document should then be forwarded to the Executive Secretary (along with the electronic file on a disk as described below). The Executive Secretary shall maintain a file with the originals of all briefing and decision memoranda. Each original decision memo should have the corresponding briefing memorandum attached in the MARC file.

2. Electronic Copies

Along with the original signed version of the document, the lead author shall send an electronic copy of the decision memorandum with the briefing memorandum attached (i.e., one WordPerfect file containing both documents) to the Executive Secretary for filing on the HED directory as per the division's SOP ("PAPER AND LAN FILE PROCEDURES"). The file will be named using the following format:

T:\HED\SARC\METABOLI*pccode*MT.MEM

The Executive Secretary will also forward the file to the IMCSB storage gate-keeper for placement in the chemical's subdirectory using the following name:

T:\HED\REVIEWS*pccode*\SAB_SARC*pccode*MT.MEM

DRAFT

Oct. 30, 2003

Criteria for Inclusion of Metabolites and/or Degradates in Risk Assessments and Tolerance Expressions

Introduction

The Metabolism Assessment Review Committee (MARC) is responsible for making recommendations on the metabolites and environmental degradates that will be included in the human dietary exposure and risk assessments as well as the metabolites to be included in the tolerance expression for foods and animal feeds. The dietary risk assessment may include drinking water, plant-based foods, and livestock commodities derived from animals that may have been directly treated with a pesticide or may have consumed pesticide-treated animal feed.

The MARC will take into consideration any pesticide transformation product that has been derived from the parent pesticide. For the sake of convenience the MARC uses the term "metabolite" to denote any plant or livestock biotransformation product. The term "degradate" is used to denote any environmental degradation product that may be present in water as a result of photodegradation, microbial degradation, hydrolysis, or other environmental processes.

The MARC takes a weight-of-evidence approach toward the determination of metabolites and degradates (M/D) to be included in the exposure and risk assessments. Numerous factors are considered when making these decisions. This document will outline the criteria considered by the committee. As the criteria are somewhat different for exposure/risk assessment and the tolerance expression definition, each will be discussed separately. Examples of the application of these criteria are provided at the end of this document.

Exposure and Risk Assessment

Metabolites and degradates that significantly contribute to the dietary risk should be included in the exposure assessment. For each metabolite/degradate to be considered to contribute significantly to the risk, two factors must be addressed: 1) the relative abundance of the metabolite/degradate in the human diet; and 2) the relative toxicity of the metabolite/degradate to the parent. The MARC takes a weight-of-evidence approach to making a determination of the significance of each metabolite or degradate in question. This approach applies to water, food, animal feed, and rotational crops. All of the metabolites that the MARC recommends for inclusion in the dietary assessment are defined as the Total Toxic Residue (TTR).

1) Relative Abundance

Major Metabolites Often those metabolites that may potentially contribute significantly to the risk assessment are those that are found in the greatest abundance. For the purposes of discussion, the MARC considers major metabolites to be those that contribute to 10% or more of the total radioactive residue (TRR) in the nature of the residue studies or environmental degradates that represent 10% or more of the applied dose in environmental fate studies.

- *Most abundance:* M/D likely to be found in commodities that are human foods (e.g., found in most matrix in metabolism studies). If the metabolite/degradate is likely to be found at relatively high levels in commodities that are human foods (as opposed to animal feeds), then the MARC will likely include it in the dietary risk assessment.
- *Less abundance:* Found in only one matrix at 10-20% of the total residue. Although a metabolite may be considered a major metabolite because it is found in one commodity at greater than 10% of the total residue, the MARC may choose not to include it if all other commodities that will be included in the assessment show non-detectable residues of the metabolite.
- *Abundance Only in Feed Item:*??
- *Levels of M/D exceeded the method limit of quantitation (LOQ) in magnitude of residue or water monitoring studies.* Occasionally a metabolite/degradate may be found in nature of the residue or laboratory studies (environmental fate), but not found, or found in very low levels, in the magnitude of residue or water monitoring or field dissipation studies. In such cases, the MARC is less likely to include it in the dietary assessment. If, however, the M/D is found in greater abundance in the magnitude of residue/water monitoring studies than was anticipated based on the nature of the residue/laboratory studies, then the MARC is more likely to include it the risk assessment.
- *Quantitation Difficulties* The MARC may make recommendations for inclusion of M/D that may not be easily quantified. In such cases, creative means may have to be used when considering them in the quantitative assessment. If sufficient background information has been presented at the meeting, the MARC may make a recommendation on the methodology to be used. Otherwise, the MARC will defer to the expertise of the Risk Assessment Team, who would be responsible for thoroughly explaining their approach in the risk assessment document.

Minor Metabolites Metabolites that comprise less than ten percent of the TRR (or applied dose in environmental studies) are classified as minor metabolites by the committee. The MARC does not typically recommend for inclusion of minor metabolites in the dietary risk assessment as they generally do not contribute significantly to the exposure assessment. However, it may be considered in the situations outlined below.

- Minor metabolites are known, or strongly suspected, to be considerably more toxic than the parent compound.
- The analytical method for data collection is a common moiety method and includes several metabolites, including minor metabolites.

Theoretical Metabolites MARC discussions may also include a discussion of metabolites/degradates that may not have been found in the nature of the residue and/or environmental fate studies, but may be theoretically possible. Such discussions usually arise when the parent compound may have a moiety that is of known toxicity, but was not identified in the submitted studies. If the MARC has such a concern, and the submitter did not attempt to identify these metabolites in the studies or did not conduct the study in a manner so that the M/D could be identified, then the MARC may request further clarification or submission of additional

studies. An example of this may include a pesticide with an aniline ring, but the aniline ring was not labeled in the metabolism study, so that identification of the free aniline would be very difficult.

2) Relative Toxicity

Three situations may occur regarding the potential toxicity of each major M/D in question: 1) the M/D is likely to have similar toxicity to the parent compound with respect to the adverse effects and the doses needed to induce those effects; 2) the M/D is not likely to induce adverse effects, unless administered at high doses.; or 3) the M/D will not likely produce similar toxic effects as the parent compound, but may produce other adverse effects at similar or lower doses.

In most cases, separate toxicity data are not available for the metabolites/degradates in question. Therefore, the MARC will make a structure/activity relationship determination using what is known about the toxicity of the parent compound, its mechanism of toxicity (if known), etc. Questions that the MARC typically considers are:

- Is the M/D structurally similar to the parent compound?
- Is the M/D likely to have toxic effects that are different from the parent but at similar doses?
- Is the structure similar to compounds with known toxicities?
- Is the M/D hydrophilic and likely to be excreted?
- Is the M/D a rat metabolite?
- If the M/D is a conjugate, is it likely to release a more toxic compound in the human digestive system?
- Has the mechanism of toxicity for the parent compound been defined?

After discussing the aforementioned questions, the committee will determine whether the M/D should be included in the exposure and risk assessment. Table 1 includes a list of considerations that outlines the factors that would make it more or less likely for the MARC to include the M/D in the risk assessment. Each of these factors is discussed below.

- *Parent Compound Toxicity.* If the metabolite in question has a similar structure to the parent compound, the MARC may consider the metabolite to have similar toxicity to the parent. The more toxic the parent compound (with regard to effects and dosage) the greater need to ensure all residues of concern are included in the assessment. Conversely, if the parent compound is low toxicity (i.e. the reference dose is very high), and the metabolite(s) in question have similar structures, and possibly similar toxicity, then the MARC is less likely to include such metabolites, particularly if including it would prove to be burdensome. Such situations include lack of exposure data, analytical method, environmental fate factors, etc.
- *Metabolite/degradate is not a rat metabolite.* If the M/D in question was not identified as a rat (mammalian) metabolite, then any toxic effect it may produce may not have been

seen in the mammalian toxicity studies. Therefore, there may be a greater need to include in the exposure/risk assessment or recommend future study with the compound.

- *Metabolite is included in Codex/Canadian or other international regulations and risk assessments.* The EPA is moving toward greater harmonization with other international bodies, including Codex and our NAFTA partners. If other international bodies include the M/D of concern in their assessments, and data submitted to the EPA indicate the M/D could contribute to the dietary risk, then the MARC is more likely to recommend inclusion of the M/D in the assessment. Conversely, if other international bodies do not include it in their assessment, and the M/D is not the most abundant residue, or not of significant toxicity concern, then the MARC is less likely to recommend its inclusion in the assessment.

Separate Assessments for Metabolites and Degradates For some chemicals, limited toxicity data may be available for the metabolites and degradates of interest, but rarely will the MARC have access to a full toxicity data set. These data occasionally indicate separate consideration in the risk assessment for the metabolite/degradate of concern. For example, the M/D may show similar effects as the parent compound, but toxicity data may suggest that lower doses of the M/D may produce the similar effect. Also, the MARC may determine that the M/D is not likely to produce adverse effects that are similar to the parent, but may have some toxicity at relevant doses in a manner different than the parent compound. In such cases the MARC may recommend a separate assessment for the M/D that would require the risk assessment team to take the information back to the HIARC for dose and endpoint selection.

Table 1. Considerations for Major (>10% of the TRR) Metabolites/Degradates to be included in the Exposure Assessment

More Likely to Be Included	Less Likely to Be Included
▸ Parent compound is highly toxic. ▸ Is not a rat metabolite. ▸ Structure is similar to the parent compound. ▸ M/D likely to be found in commodities that are human foods. ▸ Levels of M/D exceeded the method limit of quantitation (LOQ) in magnitude of residue or water monitoring studies. ▸ Metabolite is included in Codex/Canadian or other international regulations and risk assessments. ▸ Parent compound was non-detectable in metabolism studies, but metabolites were found in high levels.	▸ Found in only one matrix at 10-20% of the total residue. ▸ Is a rat metabolite, but found in greater abundance in animal feeds than commodities that are human foods. ▸ Parent compound has very low toxicity (i.e. RfD is very high). ▸

Tolerance Expression Definition

Tolerances are mainly used by monitoring Agencies as a means to detect misuse of the parent pesticide. If a tolerance is exceeded, the food may be considered adulterated and seized by the monitoring agency. Tolerances are usually set by the EPA at the highest residue level expected from the maximum legal use of the pesticide. Residues exceeding the tolerance level are likely as a result of the misuse of the pesticide and subject to investigation for pesticide use violations.

While toxicity considerations play a major role in determination of metabolites included in the exposure and risk assessment, for tolerance expression definition another factor is equally important, the degree to which the metabolite is an indicator of the misuse of the parent pesticide. The total toxic residue is the starting point for determining the metabolites that will be included in the tolerance expression. It is rare that compounds which are not in the TTR are included in the tolerance expression. On the other hand, it is quite common that not every metabolite in the TTR is included in the tolerance expression.

There are advantages and disadvantages to including every metabolite in the TTR in the tolerance expression. If enforcement agencies analyze each commodity for everything in the TTR, the monitoring data may provide considerable exposure information should the risk assessment require refining in the future. However, the metabolite of concern may not be easily determined by the monitoring agency. For example, metabolites are less frequently recovered than parent pesticides using the standardized multi-residue methods employed by most agencies. Therefore, the monitoring agency would only look for them when specialized studies, using compound-specific methods, are conducted. In light of the additional costs to the monitoring agencies, the EPA needs to weigh what additional value, or measure of protection, is obtained when such metabolites are included in the tolerance expression.

When choosing the residues to be included in the tolerance expression, the MARC will look at the total database of residue chemistry studies, focusing on the magnitude of residue and analytical methods. Table 2 includes a list of considerations that outlines the factors that would make it more or less likely for the MARC to include the metabolite in question in the tolerance expression. Each of these factors is discussed below.

- *Parent Compound Toxicity.* If the metabolite in question has a similar structure to the parent compound, the MARC may consider the metabolite to have similar toxicity to the parent. The high toxicity of the parent compound may suggest the need for a refined risk assessment, such that monitoring data (from tolerance enforcement agencies) for the metabolite may be very helpful in the future. Conversely, if the parent compound is low toxicity (i.e. the reference dose is very high), and the metabolite(s) in question have

similar structures, and possibly similar toxicity, then the MARC is less likely to include such metabolites.

- *Multi-residue methods.* The MARC must take into consideration the ability of enforcement agencies to determine the metabolites in question. Occasionally the ability of the standard multi-residue methods to determine a metabolite is a factor in the discussions about whether to include a metabolite in the tolerance expression. In a given situation where there are relatively equal arguments for both including and excluding metabolites from the tolerance expression, and the metabolite cannot be determined using the standard multi-residue methods, then the MARC is less likely to include the metabolite in the tolerance expression.
- *Analytical Enforcement Methodology.* If the parent and metabolite(s) cannot be determined by the standard multi-residue methods, and the proposed enforcement method is a common moiety method such that the parent and metabolites cannot be determined individually, then the MARC is more likely to include the metabolites. Enforcement agencies would have no way to distinguish between residues of parent or metabolites. If the metabolites were not included then a violative situation could exist if the total residues of parent and metabolites (from the legal use of the pesticide) would exceed the tolerance based on parent alone.
- *Relative concentrations of parent compound and metabolites.* The tolerance expression must be able to be used as an indicator of misuse. To that end, it is best to include those analytes that are likely to be found in the greatest concentration in/on commodities in question. If metabolites are of toxicity concern, but their concentrations are much less than that of the parent compound, then there is not as great a need to include them in the tolerance expression, since the parent compound would be a sufficient indicator. Conversely, if the metabolism and magnitude of residue studies show that metabolites are more likely to be found in greater abundance than the parent compound, then the MARC is more likely to include them in the tolerance expression. On rare occasions the MARC may include a metabolite even if there is no toxicity concern because it may be a better indicator of misuse than the parent compound. For crops that have multiple commodities that are regulated, but a metabolite in question is only found in one matrix, the MARC is less likely to include that metabolite. If however, the metabolite is found in only one commodity that is a high-consumption human food, and the MARC has toxicity concerns, then the MARC is more likely to include the metabolite.
- *International Regulations.* The MARC is more likely to include metabolites that are included in the maximum residue limit expression for trading partners, Codex, or other international bodies as a means to facilitate trade. Conversely, if the MARC is considering inclusion of a metabolite that is not included in the expression of Codex or other international bodies, then the MARC will provide a detailed justification on the need to include the metabolite.

Table 2. Considerations for Major (>10% of the TRR) Metabolites to be Included in the Tolerance Expression

More Likely to Be Included	Less Likely to Be Included
▸ Parent compound is highly toxic. ▸ Multi-residue methods are able to recover and detect metabolite. ▸ Proposed enforcement method is a common moiety method **and** metabolite cannot be analyzed by a multi-residue method. ▸ Concentrations in commodities are likely to be much greater than the parent compound. ▸ Structure is similar to the parent compound. ▸ Parent compound is non-detectable. ▸ Metabolite likely to be found in commodities that are human foods. ▸ Levels of metabolite exceeded the method limit of quantitation (LOQ) in magnitude of residue studies. ▸ Metabolite is included in Codex/Canadian or other international regulations.	▸ Found in only one matrix at 10-20% of the total residue. ▸ Parent compound has very low toxicity (i.e. RfD is very high). ▸ Codex or other international bodies do not include metabolite in regulations. ▸ Metabolite cannot be determined by multi-residue methods.

APPENDIX 1
Examples of MARC Decisions

Example 1. Parent Only; surface residues, little background

Example 2. Parent Only, but some metabolites found

Example 3. RA is parent + metabolites, TE is parent only

Example 4. RA & TE includes metabolites

Example 5. Dimethoate - separate dose for omethoate, need consideration of metabolites.

Norman Birchfield

11/20/03 02:05 PM

To: Edward Odenkirchen/DC/USEPA/US@EPA
cc: Ingrid Sunzenauer/DC/USEPA/US@EPA, Steven Bradbury/DC/USEPA/US@EPA
Subject: MARC criteria document and SOP

Hi Ed

Here are the current MARC SOP (1998) and the current draft under consideration including the consideration of DW water. The SOP is intended to provide directions to the risk assessment team on what to present to the MARC. The draft criteria document, very similar to what you saw before, describes how MARC makes its decision. It is also attached.

At the moment the SOP states that metabolite toxicity data from "computerized databases" should be included but the specific databases are not mentioned. Next Tuesday we should have a more final list of the specific databases that are searched by HED for metabolite toxicity which can be added to the SOP and the criteria documents. Right now the incomplete list of information